Multiple Sclerosis and Related Disorders 48 (2021) 102694

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Prevalence of adverse pregnancy outcomes after exposure to interferon beta prior to or during pregnancy in women with MS: Stratification by maternal and newborn characteristics in a register-based cohort study in Finland and Sweden

Marta Korjagina [a], Katja M Hakkarainen [b,*], Sarah Burkill [c], Yvonne Geissbühler [d], Meritxell Sabidó [e], Nicholas Everage [f], Kiliana Suzart-Woischnik [g], Riho Klement [h], Jan Hillert [i], Auli Verkkoniemi-Ahola [j], Shahram Bahmanyar [k,l,m], Scott Montgomery [n,o,p], Pasi Korhonen [q], European Interferon Beta Pregnancy Study Group and the Nordic MS Pregnancy & Interferon Beta study group

[a] StatFinn-EPID Research, Paldiski mnt 29, 10612, Tallinn, Estonia
[b] StatFinn-EPID Research, Prästgårdsgatan 28, 431 44 Mölndal, Sweden
[c] Karolinska Institute, Solnavägen 1, 171 77 Solna, Sweden
[d] Novartis Pharma AG, Evidence and Launch Excellence, Asklepios 8-3, Postfach, CH-4002 Basel, Switzerland
[e] Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
[f] Biogen, 225 Binney Street, Cambridge, MA 02142, United States
[g] Bayer AG, Building S102, 148, 13353 Berlin, Germany
[h] StatFinn-EPID Research, Narva maantee 3, 51009 Tartu, Estonia
[i] Karolinska Institute, Tomtebodavägen 18A, 171 77 Stockholm, Sweden
[j] Clinical Neurosciences, Neurology, Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, 00029, Helsinki, Finland
[k] Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Solnavägen 1, 171 77 Solna, Sweden
[l] Centre for Psychiatry Research, Karolinska Institutet, Norra Stationsgatan 69, floor 7, 113 64 Stockholm, Sweden
[m] Stockholm Health Care Services, Solnavägen 1 E, Stockholm, Sweden
[n] Clinical Epidemiology Division, Department of Medicine, Karolinska Institute, Solnavägen 1, 171 77 Solna, Sweden
[o] Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University Hospital and Örebro University, Fakultetsgatan 1, 701 82 Örebro, Sweden
[p] Department of Epidemiology and Public Health, University College London, London, United Kingdom
[q] StatFinn-EPID Research, Metsänneidonkuja 6, 02130 Espoo, Finland

ARTICLE INFO

Keywords:
Multiple sclerosis
Interferon-beta
Pregnancy
Adverse pregnancy outcomes
Stratification

ABSTRACT

Background: Previous studies reported no increase in the prevalence of adverse pregnancy outcomes after exposure to interferon-beta (IFN-beta). However, no study has investigated if the prevalence of these outcomes after IFN-beta exposure is modified by maternal and newborn characteristics. Our objective was to describe the stratified prevalence of adverse pregnancy outcomes among women with multiple sclerosis (MS) exposed only to IFN-beta or unexposed to any MS disease modifying drugs (MSDMDs).

Methods: This population-based cohort study using Finnish (1996-2014) and Swedish (2005-2014) register data included pregnancies of women with MS exposed only to IFN-beta 6 months before or during pregnancy (n=718) or unexposed to MSDMDs (n=1397). The outcome prevalences were described stratified by maternal and newborn characteristics, with 95% confidence intervals (CIs). Confounder-adjusted analyses were performed if the prevalence results indicated modified effect of IFN-beta in specific strata.

Results: The stratified analysis indicated that the prevalence of serious (anomaly or stillbirth) and other adverse pregnancy outcomes was similar among the exposed and unexposed, with no statistically significant difference. Among women treated for MS >5 years, serious adverse pregnancy outcomes occurred in 4.3% (95%CI: 1.9-8.3%) of pregnancies exposed only to IFN-beta 6 months before or during pregnancy and in 2.7% (95%CI: 1.2-5.0%) of unexposed pregnancies. The confounder adjusted analyses did not support the hypothesis that MS

* Corresponding author at: StatFinn – EPID Research, Prästgårdsgatan 28, 431 44 Mölndal, Sweden.
E-mail address: katja.hakkarainen@iqvia.com (K.M. Hakkarainen).

https://doi.org/10.1016/j.msard.2020.102694
Received 14 August 2020; Received in revised form 6 November 2020; Accepted 13 December 2020
Available online 16 December 2020

treatment duration before pregnancy would modify the risk of adverse pregnancy outcomes after exposure to IFN-beta 6 months before or during pregnancy.
Conclusion: The prevalence of adverse pregnancy outcomes was not increased after IFN-beta exposure, when pregnancies of women with MS were stratified by maternal and newborn characteristics. The stratified results were similar to the unstratified results in the same population.

1. Introduction

Multiple sclerosis (MS) is the most common chronic neurological disease in women of childbearing age, with treatment initiation recommended at an early disease stage (Banwell et al., 2019). Among several MS disease-modifying drugs (MSDMDs) that have been approved (Ransohoff et al., 2015), interferon-beta (IFN-beta) (European Medicines Agency EMA, 2019a; European Medicines Agency EMA, 2019b; European Medicines Agency EMA, 2019c; European Medicines Agency EMA, 2019d; European Medicines Agency EMA, 2020a) has been used to treat MS for the last 20 years (Montalban et al., 2018) with favourable benefit-risk profiles. Since September 2019, IFN-beta use may be considered during pregnancy, if clinically needed (European Medicines Agency EMA, 2019a; European Medicines Agency EMA, 2019b; European Medicines Agency EMA, 2019c; European Medicines Agency EMA, 2019d; European Medicines Agency EMA, 2020a).

Previous observational studies (Thiel et al., 2016; Hellwig et al., 2012; Romero et al., 2015; Coyle et al., 2014; Sandberg-Wollheim et al., 2011; Amato et al., 2010; Weber-Schoendorfer and Schaefer, 2009; Patti et al., 2008; Hellwig et al., 2020a; Hellwig et al., 2020b) and a large post-authorisation safety study (PASS) (EPID Multiple Sclerosis Pregnancy study, 2020) in women with MS have reported no increase in the

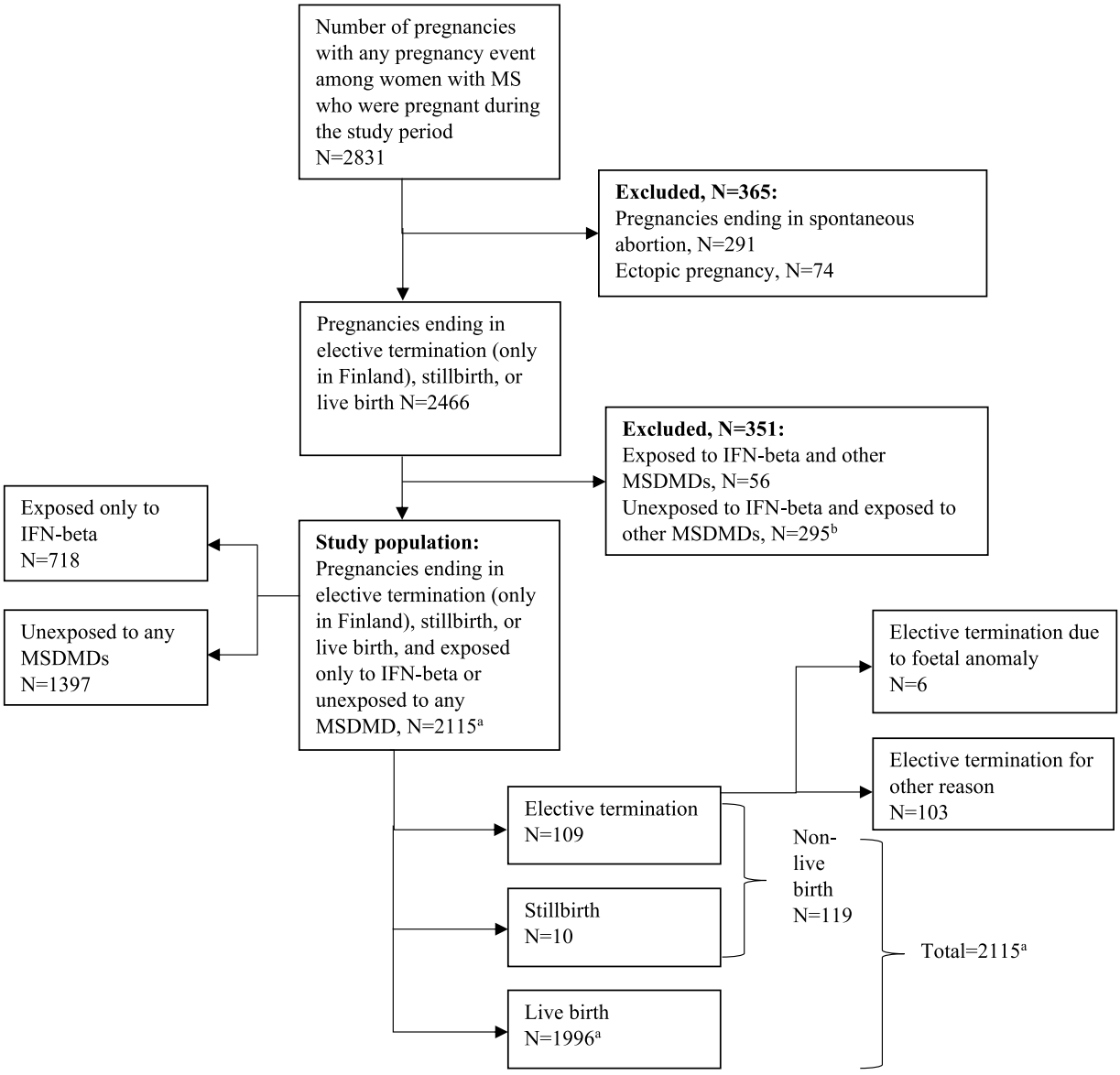


Fig. 1. Included pregnancy outcome events.
[a]Used as a denominator in this study.
[b]Contributed to the alternative unexposed group: unexposed to IFN-beta regardless of exposure to other MSDMDs, N=1692 (Unexposed to any MSDMDs, N=1397 + Unexposed to IFN-beta and exposed to other MSDMDs, N=295).

Table 1
Maternal characteristics for the pregnancy outcome events ending in elective termination (only in Finland), stillbirth, or live birth, which were exposure only to IFN-beta 6 months before or during pregnancy or unexposed to any MSDMDs

Maternal characteristics	Pregnancy outcome events ending in elective termination (only in Finland), stillbirth, or live birth
Pregnancy events, N	2115
Country of residence	
Finland, n (%)	769 (36.4)
Sweden, n (%)	1346 (63.6)
Year of pregnancy outcome	
1996-1999, n (%)	45 (2.1)
2000-2004, n (%)	58 (2.7)
2005-2009, n (%)	675 (31.9)
2010-2014, n (%)	1337 (63.2)
Maternal age at LMP	
≤20 years, n (%)	20 (0.9)
21-25 years, n (%)	219 (10.4)
26-30 years, n (%)	688 (32.5)
31-35 years, n (%)	819 (38.7)
36-40 years, n (%)	327 (15.5)
> 40 years, n (%)	42 (2.0)
Mean (± SD)	31.2 (4.6)
Any chronic disease before or during pregnancy (excl. MS)[a], n (%)	798 (37.7)
Exposure to any teratogenic medications before[b] or during pregnancy[c]	
group C, n (%)	1202 (56.8)
group D, n (%)	302 (14.3)
Time since MS diagnosis	
≤2 years, n (%)	616 (29.1)
3-5 years, n (%)	718 (33.9)
>5 years, n (%)	781 (36.9)
Mean, years (± SD)	4.5 (3.7)
Duration of MS treatment[d]	
≤2 years, n (%)	777 (36.7)
3-5 years, n (%)	578 (27.3)
>5 years, n (%)	525 (24.8)

IFN-beta, interferon beta; MS, multiple sclerosis; n, number of pregnancy outcome events; MSDMD, multiple sclerosis disease modifying drug; LMP, last menstrual period; MS, multiple sclerosis; SD, standard deviation.

[a] List of chronic diseases (excl. MS) listed in Appendix A.3.

[b] Six months before LMP.

[c] Teratogenic C and D drugs are based on year 2017 list in Sweden (Appendix A.4).

[d] Duration of MS treatment at LMP refers to refers to any MS treatment the patient may have ever received.

prevalence of adverse pregnancy outcomes after exposure to IFN-beta before or during pregnancy. Data from Finland, however, suggest that the prevalence of elective terminations for reasons other than foetal anomaly may be increased among pregnant women exposed to IFN-beta (EPID Multiple Sclerosis Pregnancy study, 2020). No prior study has investigated the prevalence of adverse birth outcomes among IFN-beta exposed women stratified into subgroups by maternal and newborn characteristics, apart from describing them as risk factors of adverse pregnancy outcomes (Amato et al., 2010; World Health Organization, 2016). Stratified analyses would inform whether the prevalence of adverse pregnancy outcomes after IFN-beta exposure is modified by certain maternal characteristics or if the prevalence by exposure status differs according to newborn characteristics.

The objective of this large population-based cohort study, using register data, was to describe the prevalence of adverse pregnancy outcomes among pregnancies of women with MS exposed only to IFN-beta and those unexposed to any MSDMD, with stratification by maternal and newborn characteristics.

2. Material and methods

2.1. Study design, setting, and participants

This cohort study was part of the recently conducted PASS (EPID Multiple Sclerosis Pregnancy study, 2020), utilising national registers in Finland and Sweden. The data were extracted on women with MS (International Classification of Diseases 10th revision; ICD-10 code G35) who were pregnant during the study period: 01 January 1996 – 31 December 2014 in Finland and 01 July 2005 – 31 December 2014 in Sweden. Pregnancies ending in elective termination (only in Finland), stillbirth, or live birth during the study period were included in this cohort study population. Ectopic pregnancies and spontaneous abortions, included in the main analysis of the PASS (EPID Multiple Sclerosis Pregnancy study, 2020), were excluded from this study population due to incomplete information on key variables, including gestational age, and due to the inability to detect all spontaneous abortions using healthcare data. Most early spontaneous abortions do not involve an interaction with healthcare, and, thus are not recorded. Late spontaneous abortions might be managed in primary care, which is not included in the used registries. Exclusively, pregnancies for which exposure status (as defined below) could be defined were included. If women had multiple pregnancy events during the study period or multifetal gestations, all pregnancies, births, and foetuses were included, the exposure status was defined separately for each pregnancy, and the outcomes of each foetuses were considered separately. The study was approved by the Helsinki University Hospital Ethics Committee (Finland; 159/13/03/00/2016) and the Regional Ethical Review Board in Stockholm (Sweden; 2016/874-31/2).

2.2. Data sources and data linkage

Extracted data from the healthcare registers were linked with a unique personal identification number. The healthcare registers included the Care Register for Health Care (Finnish Institute for Health and Welfare THL, 2016), Medical Birth Register (Finnish Institute for Health and Welfare THL, 2019), Register on Induced Abortions (Finnish Institute for Health and Welfare THL, 2020a), Register of Congenital Malformations (Finnish Institute for Health and Welfare THL, 2020b), Special Reimbursement Register (SRR) (Social Insurance Institution (Kela), 2020a), and National Prescription Register (Social Insurance Institution (Kela), 2020b) in Finland, and the National Patient Register (National Board of Health and Welfare (Socialstyrelsen), 2019a), Medical Birth Register (National Board of Health and Welfare (Socialstyrelsen), 2019b), Swedish Prescribed Drug Register (SPDR) (Wettermark et al., 2007), and Swedish MS Register (Hillert and Stawiarz, 2015) in Sweden.

2.3. Variables

2.3.1. Exposure

Pregnant women were considered exposed only to IFN-beta if an IFN-beta product (with Anatomical Therapeutic Chemical codes L03AB07, L03AB08, L03AB13) had been dispensed from the pharmacy, without any dispensation of another MSDMD (Appendix A.1), within 6 months before the last menstrual period (LMP) or during pregnancy. In Finland, dispensed drugs were captured from the SRR, and in Sweden from the SPDR and the Swedish MS Register. Including dispensations 6 months before LMP enabled capturing exposure within 3 months of LMP, as patients in Finland and Sweden are typically dispensed chronic medications in 3-month intervals. Women without dispensation of an IFN-beta product or any another MSDMD in the 6 months prior to LMP or during pregnancy were considered unexposed, with a prolonged purchase period of 9 months before LMP for mitoxantrone and cladribine tablets.

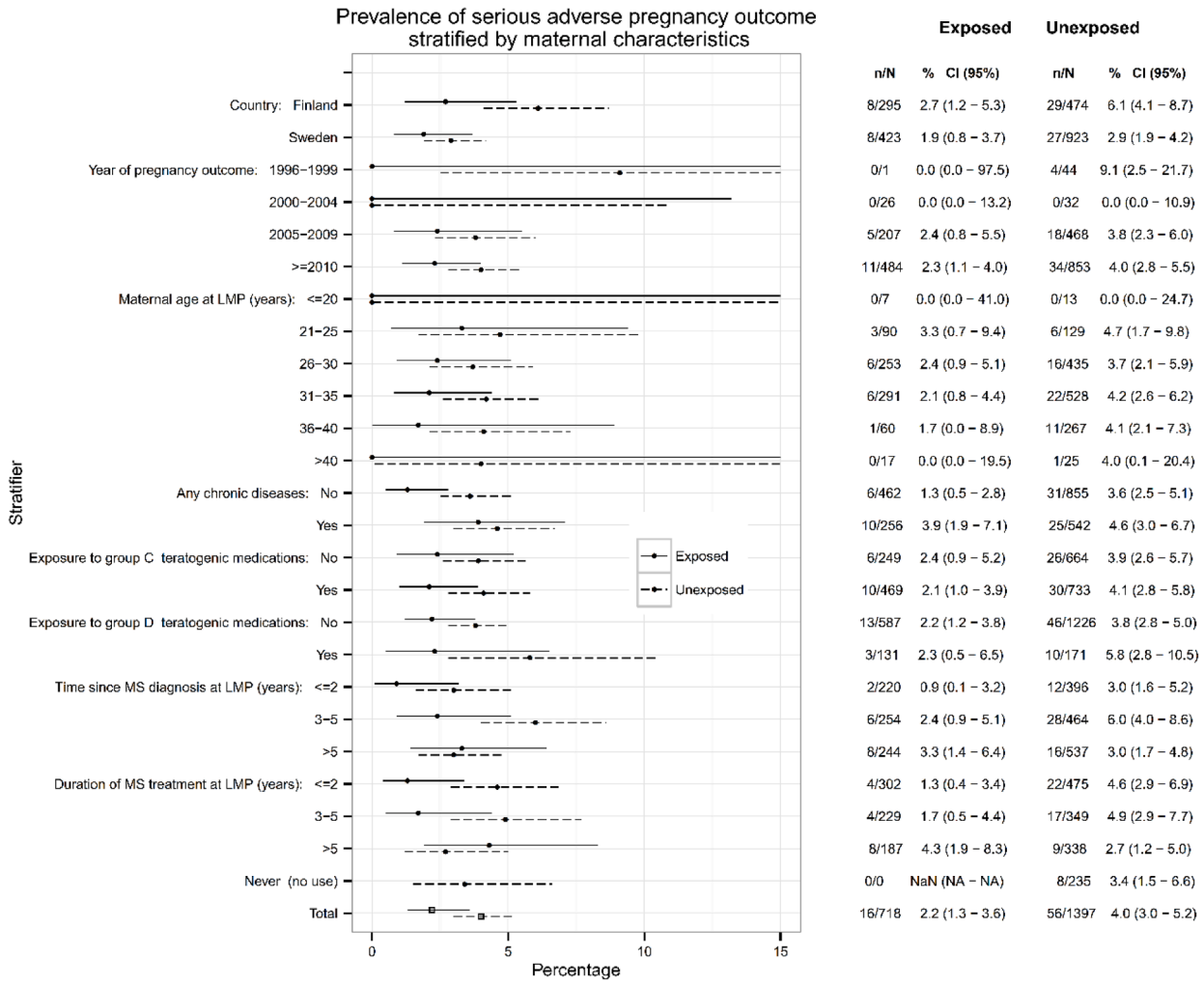


Fig. 2.1. Prevalence of *serious adverse pregnancy outcomes* (IFN-beta only exposed N=718 pregnancies; unexposed N=1397 pregnancies) stratified by **maternal characteristics**, among pregnancies exposed only to IFN-beta 6 months or during pregnancy and among those unexposed to any MSDMDs.

2.3.2. Outcomes

The primary outcome variable was the composite *serious adverse pregnancy outcome*, defined as elective termination of pregnancy due to foetal anomaly (TOPFA), or live birth with a major congenital anomaly (MCA), or stillbirth. Of other outcomes, *MCA total* included TOPFA, MCA in live births, and also MCA in stillbirths but excluded other stillbirths. Other outcomes were *MCA in live births* only; *elective termination for reasons other than foetal anomaly; TOPFA* only; *stillbirth* only; and *non-live birth* (combining elective terminations for any reasons and stillbirths). MCA was defined as ICD codes (9th revision; ICD-9) 740-759, divided into 25 groups, with minor anomalies excluded according to the European Surveillance of Congenital Anomalies (EUROCAT). For live births, the MCA diagnosis was followed-up for 12 months in Finland and 6 months in Sweden. Stillbirths were defined as the death of foetus with birth weight of ≥500 grams or ≥22+0 gestational weeks, and elective termination as ICD-10 code O04 (available only in Finland).

2.3.3. Maternal and newborn characteristics

The maternal characteristics used for stratification (Appendix A.2) were country of residence, year of pregnancy outcome, maternal age at LMP, time since MS diagnosis, duration of MS treatment, any chronic diseases (Appendix A.3), and exposure to any teratogenic medications (Appendix A.4). As described in Appendix A.2, the duration of MS treatment was defined as the time in years between the start of any MSDMD treatment (IFN-beta or another MSDMD, as in Appendix A.1) and LMP, regardless of exposure status 6 months before or during pregnancy. The newborn characteristics (Appendix A.2) included gestational age at pregnancy outcome and birth weight, which were reported for pregnancy outcomes other than elective terminations. The stratification variables were pre-defined in the study protocol (EPID Multiple Sclerosis Pregnancy study, 2020), which was registered before the analyses.

2.4. Statistical analyses

The number and point prevalence (%) of the study outcomes were described for pregnancies exposed only to IFN-beta and unexposed to any MSDMD, and stratified by the maternal and newborn characteristics (EPID Multiple Sclerosis Pregnancy study, 2020). Stratification by maternal characteristics was performed for all outcomes, and stratification by newborn characteristics for outcomes other than elective terminations. The prevalence was presented with 95% confidence intervals (CI) using the Pearson-Clopper method. When the 95% CIs for the prevalence estimates for the exposed and unexposed pregnancies overlapped within a stratum, the outcome prevalence was considered not to differ with statistical significance between the exposed and unexposed pregnancies in that stratum. All results are reported per pregnancy outcome event (Appendix A.5). A missing category was included in the

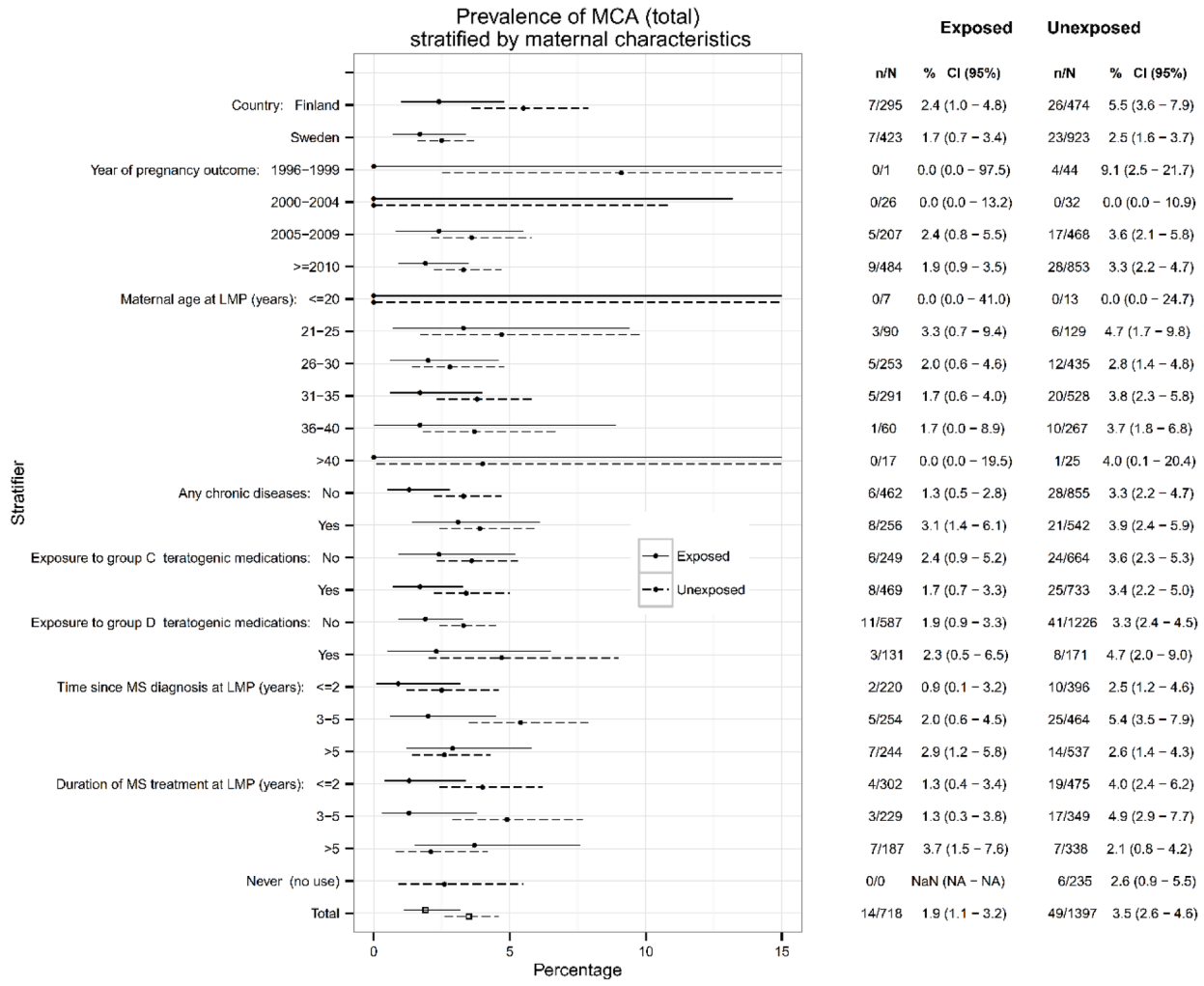


Fig. 2.2. Prevalence of *MCA total* (IFN-beta only exposed N=718 pregnancies; unexposed N=1397 pregnancies) stratified by **maternal characteristics**, among pregnancies exposed only to IFN-beta 6 months or during pregnancy and among those unexposed to any MSDMDs.
CI, confidence interval; IFN-beta, interferon beta; LMP, last menstrual period; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy outcome events.

analysis for variables with missing data. In further analyses, an alternative definition of the unexposed pregnancies was used, wherein we considered pregnancies unexposed to exclusively IFN-beta instead of pregnancies unexposed to *any* MSDMDs.

Additional confounder adjusted *post hoc* analyses further investigated whether the effect of IFN-beta exposure is modified by maternal characteristics, as detailed in Appendix A.6. The analyses were considered for the most prevalent outcomes if effect modification was suspected due to differing pattern of point prevalences for an adverse pregnancy outcome among the exposed and unexposed, when comparing the results in strata of a maternal characteristic to the unstratified results (Hakkarainen et al., 2020).

2.5. Data statement

According to the registered study protocol (EPID Multiple Sclerosis Pregnancy study, 2020), access to the study data cannot be given to any third parties, and the study data cannot be used for purposes other than described in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

3. Results

The study population included 2,115 pregnancies ending in elective termination (only in Finland), stillbirth, or live birth (Fig. 1), and being exposed only to IFN-beta (n=718) or unexposed to any MSDMDs (n=1,397). The maternal age at LMP was most commonly within the age group of 31-35 years (38.7%) (Table 1). Other chronic diseases before or during pregnancy were reported in 37.7% of the pregnancies. The time since MS diagnosis and time since the start of any MSDMD treatment before the pregnancy was >5 years in 36.9% and 24.8% of the pregnancies, respectively.

3.1. Maternal characteristics

When stratifying by maternal characteristics, the prevalence of the primary outcome (i.e. composite *serious adverse pregnancy outcome*) was similar among pregnancies exposed only to IFN-beta and those unexposed to any MSDMDs, with no statistically significant difference, as indicated by the overlapping 95% CIs for the prevalence estimates (Fig. 2.1). Within each stratum except for the women treated for MS >5 years, the point prevalence of the composite primary outcome was lower among pregnancies exposed only to IFN-beta compared to the unexposed women; however, the comparisons were not statistically

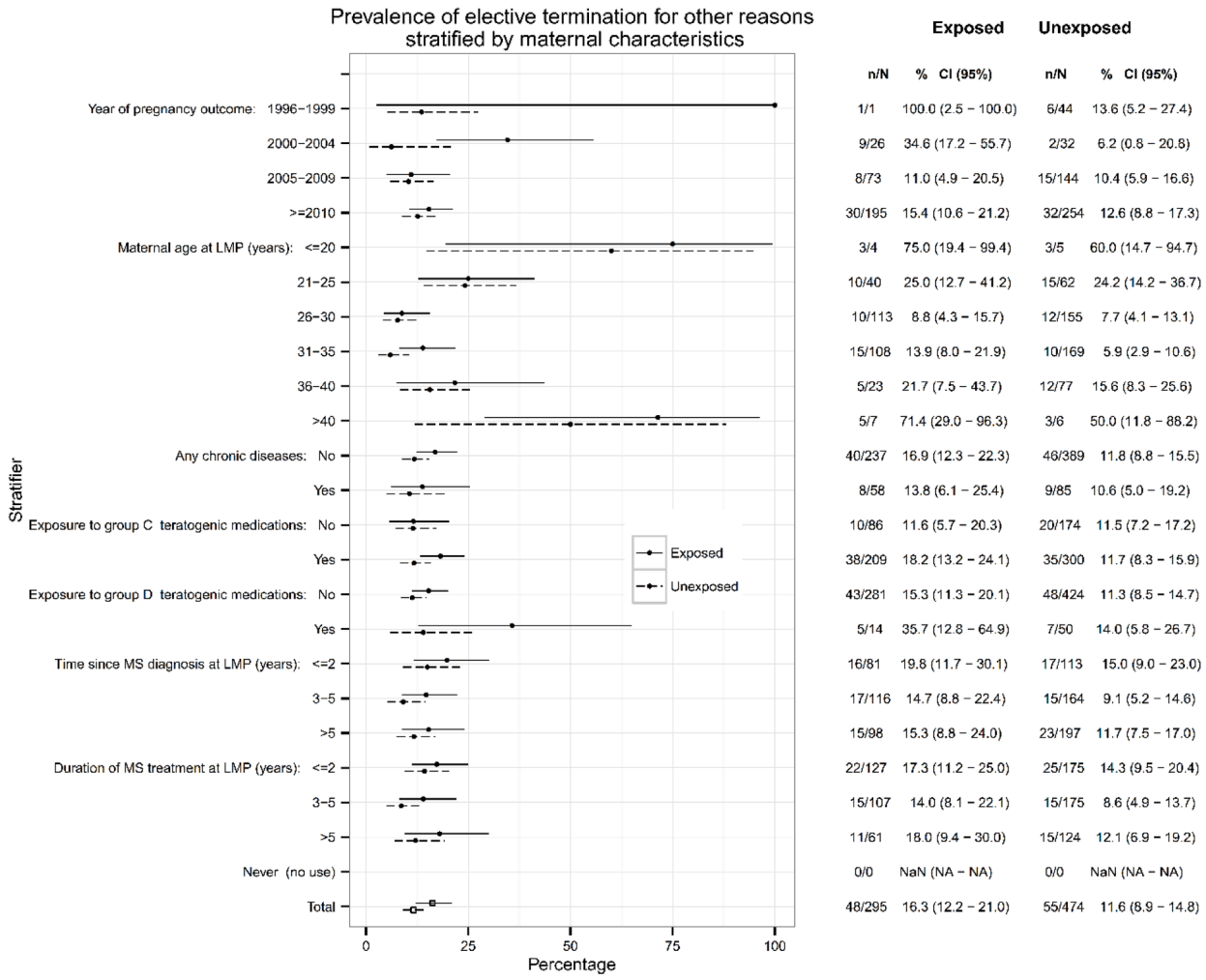


Fig. 2.3. Prevalence of *elective terminations for other reasons than foetal anomaly* (IFN-beta only exposed N=295 pregnancies; unexposed N=474 pregnancies; data available exclusively in Finland) stratified by **maternal characteristics**, among pregnancies exposed only to IFN-beta 6 months or during pregnancy and among those unexposed to any MSDMDs.
CI, confidence interval; IFN-beta, interferon beta; LMP, last menstrual period; MS, multiple sclerosis; n, number of pregnancy outcome events.

significant. Among women treated for MS >5 years, *serious adverse pregnancy outcomes* occurred in 4.3% (95% CI: 1.9-8.3%) of pregnancies exposed only to IFN-beta and in 2.7% (95% CI: 1.2-5.0%) of pregnancies unexposed to any MSDMDs. When stratifying by maternal age, the point prevalence for the composite outcome appeared to decrease with increasing age among pregnancies exposed only to IFN-beta and was similar across the age groups among the unexposed pregnancies, however, overlapping CIs indicate no statistical difference of the observed trend.

The descriptive prevalence of *MCA total* was similar between the pregnancies exposed only to IFN-beta and unexposed to any MSDMDs when stratified by maternal characteristics (Fig. 2.2), with a trend within each stratum towards lower point prevalence among pregnancies exposed to IFN-beta compared to those which were the unexposed. The prevalence of *MCA total* among women treated for MS >5 years was 3.7% (95% CI: 1.5-7.6%) for the pregnancies exposed only to IFN-beta, and 2.1% (95% CI: 0.8-4.2%) for those unexposed to any MSDMDs. The prevalence of *MCA in live births* stratified by maternal characteristics (Appendix Fig. B.1) was consistent with those for *MCA total*.

The point estimate for the prevalence of *elective termination for other reasons than foetal anomaly* was higher among pregnancies exposed only to IFN-beta than among pregnancies unexposed to any MSDMDs in most of the maternal characteristics strata, although the comparisons were not statistically significant (Fig. 2.3). During 2000-2004, *elective terminations for reasons other than foetal anomaly* were particularly frequent among the pregnancies exposed to only IFN-beta (34.6%, 95% CI: 17.2-55.7%) vs unexposed (6.2%, 95% CI: 0.8-20.8%). In the years 1996-1999, one pregnancy was exposed to only IFN-beta and the pregnancy was terminated (100.0%), but the presence of only one case led to very low precision (95% CI: 2.5-100.0%). For elective *TOPFA*, the stratification also led to a low number of outcomes per stratum, and thereby a low precision (wide 95% CIs) of the prevalence estimates (Appendix Fig. B.2).

In the strata of varying maternal characteristics, the prevalence of *stillbirths* was similar between the pregnancies exposed only to IFN-beta and those unexposed to any MSDMDs. It is worth noticing that the total number of stillbirth cases was low (n=10), which is reflected in the low number and prevalence of *stillbirths* for several strata (Fig. 2.4). The prevalence of *non-live births*, across the strata, appeared increased for the IFN-beta exposed pregnancies (Appendix Fig. B.3).

3.2. Newborn characteristics

When stratifying by newborn characteristics, the prevalence of the composite *serious adverse pregnancy outcome* (Fig. 3.1), *MCA total* (Fig. 3.2), and *MCA in live births* (Appendix Fig. C.1) was similar among

pregnancies exposed only to IFN-beta and those unexposed to any MSDMDs, with no statistically significant differences between the two exposure groups. In the strata of newborns with gestational age of <28 and ≥37 weeks, the point prevalence of the composite outcome, *MCA total*, and *MCA in live births* appeared lower among pregnancies exposed only to IFN-beta compared to pregnancies unexposed to any MSDMDs. In the stratum of newborns with gestational age of 28-36 weeks, the point prevalence of these outcomes appeared higher when pregnancies were exposed only to IFN-beta than for pregnancies unexposed to any MSDMDs; however, few outcomes in the stratum led to poor precision (*serious adverse pregnancy outcome*, n=3, 7.1% (95% CI: 1.5-19.5%) vs n=5, 4.8% (95% CI: 1.6-10.8%); *MCA total*, n=3, 7.1% (95% CI: 1.5-19.5%) vs n=4, 3.8% (95% CI: 1.0-9.5%); *MCA in live births*, n=3, 7.1% (95% CI: 1.5-19.5%) vs n=3, 3.8% (95% CI: 1.1-9.6%)).

The prevalence of *stillbirths* (Fig. 3.3) and *non-live births* (Appendix Fig. C.2), stratified by newborn characteristics, also appeared to be similar between the pregnancies exposed only to IFN-beta and those unexposed to any MSDMDs. However, the strata had very few outcomes considering that in total only 2 stillbirths were observed among the 718 exposed and 8 stillbirths among the 1397 unexposed pregnancies.

3.3. Analysis with an alternative definition of unexposed

In the analyses using the alternative definition of unexposed, the stratified prevalence of adverse pregnancy outcomes remained consistent with the main analyses (Appendix Tables D1-D7).

3.3.1. Post hoc analyses

The *post hoc* analyses were performed for the maternal characteristic 'duration of MS treatment', which was the only characteristic that was suspected to potentially modify the effect of exposure to IFN-beta, for the following outcomes: *serious adverse pregnancy outcomes, MCA total*, and *MCA in live births*. Firstly, the likelihood ratio test demonstrated statistically significant interaction between 'duration of MS treatment' and exposure status (p-values for *serious adverse pregnancy outcome* 0.023; *MCA total* 0.027; *MCA in live births* 0.025), which indicated that 'duration of MS treatment' might modify the effect of the outcomes, i.e. that the prevalence of *serious adverse pregnancy outcomes, MCA total*, and *MCA in live births* might differ based on the duration of the mother's MS treatment before pregnancy.

Secondly, when an interaction between the exposure status (exposed to IFN-beta only or unexposed to any MSDMDs 6 months before or during pregnancy) and 'duration of MS treatment' was assessed in the entire study population (adjusted model with an interaction term), the ORs for the outcomes showed a gradual increase with an increase in the duration of MS treatment among pregnancies exposed to IFN-beta only 6 months before or during pregnancy, as compared to those unexposed to any MSDMDs 6 months before or during pregnancy wherein the mother had been treated for MS for ≤2 years before pregnancy (Appendix Table D8). The trend was opposite for the pregnancies unexposed to any MSDMDs 6 months before or during pregnancy: the ORs for the outcomes were lower when the mother had been treated for MS for >5 years before pregnancy, compared with being treated for ≤2 years before pregnancy. In these adjusted models with the interaction terms, however, the 95% CIs for all of the ORs were wide and overlapped with each other, which indicates low precision and high uncertainty in the observed effects of the duration of the mother's MS treatment before pregnancy.

Thirdly, when the exposed vs unexposed pregnancies were compared separately within each stratum of 'duration of MS treatment', the adjusted ORs for the outcomes *serious adverse pregnancy outcomes, MCA total*, and *MCA in live births* were comparable between the two strata with shorter treatment durations before the pregnancy, i.e. ≤2 years and 3-5 years (Appendix Table D9). For all of these outcomes, there was an increase in the ORs within the stratum of women with MS who had been treated for >5 years before the pregnancy. However, the wide and overlapping 95% CIs associated with their ORs do not support this increase in the outcome prevalence in the stratum with the longest treatment duration would have been statistically significant.

4. Discussion

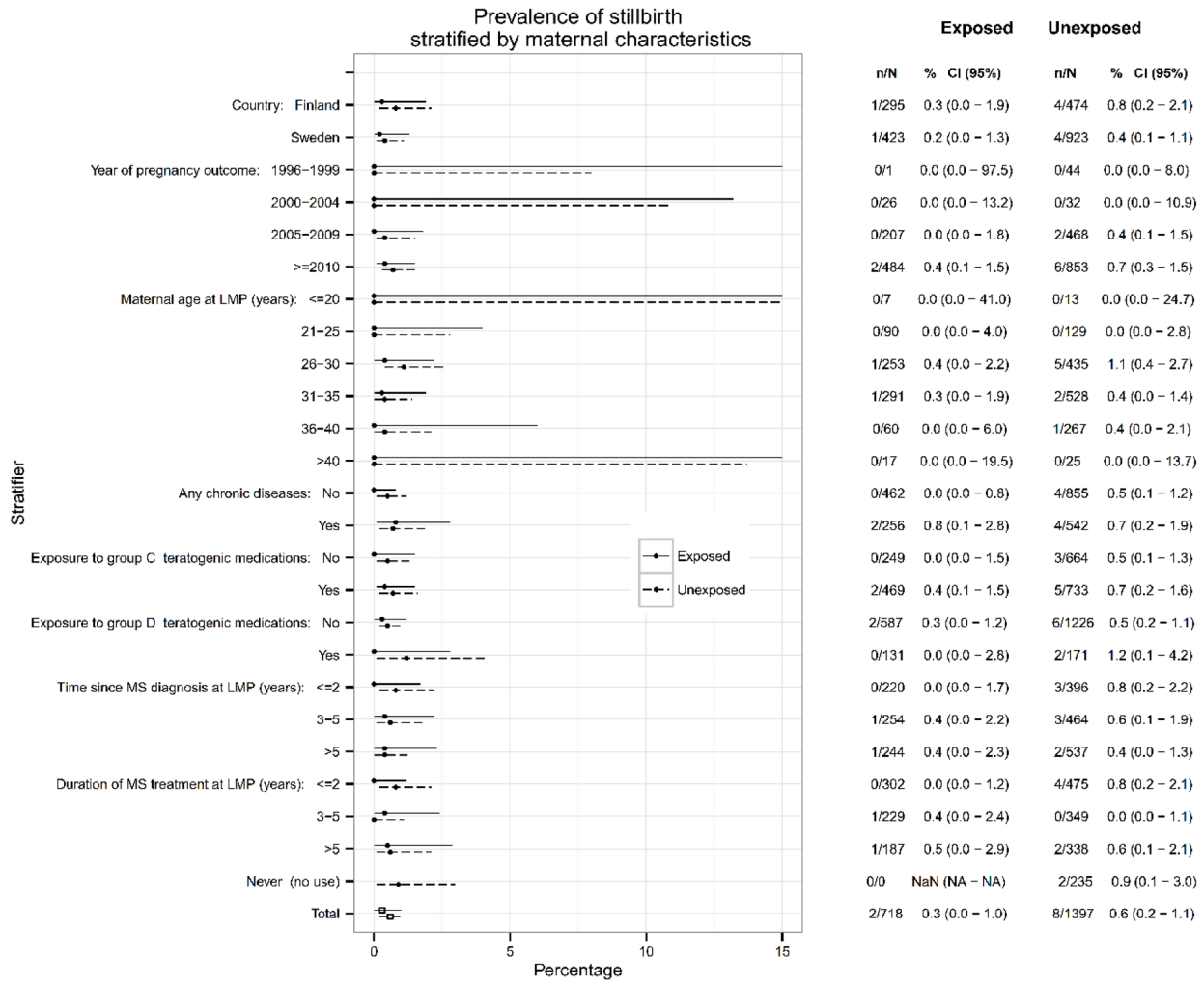
After stratification by maternal and newborn characteristics, the descriptive prevalence of serious adverse pregnancy outcomes or other pre-specified outcomes did not appear higher with IFN-beta exposure before or during pregnancy relative to those unexposed to any MSDMDs.

4.1. Maternal characteristics

Our result indicated that the descriptive prevalence of serious and other adverse pregnancy outcomes was not increased among pregnancies exposed to IFN-beta in the strata of maternal characteristics, which is consistent with the unstratified results in the same population (EPID Multiple Sclerosis Pregnancy study, 2020; Hakkarainen et al., 2020). The finding that in some strata the prevalence appeared decreased among the pregnancies exposed only to IFN-beta compared to pregnancies unexposed to any MSDMDs, without statistical significance, may have been caused by underlying factors that were unfavourable among the unexposed women and that this study using the available register data could not detect (e.g., life-style factors (beyond BMI), maternal alcohol and substance use, or actual use of teratogenic drugs before and during pregnancy). Overall, this PASS was designed to assess the safety of IFN-beta use during pregnancy and to detect the possible increase of adverse outcomes, with pre-defined objectives and analyses (EPID Multiple Sclerosis Pregnancy study, 2020). Thus, interpretations focus on a possible increase in the prevalence of adverse pregnancy outcomes.

Although the descriptive prevalence of elective terminations for reasons other than foetal anomaly appeared to be higher among exposed pregnancies across the strata of maternal characteristics, the overlapping CIs for the exposed and unexposed indicate no statistically significant difference. In general, reasons for such elective terminations, available exclusively from Finland, include social reasons, such as either young or old age, and medical reasons related to the foetus or a parent (Väisänen, 2015). The high frequency of elective terminations for reasons other than foetal anomaly among the IFN-beta exposed pregnancies in years 2000-2004 and 1996-1999 probably attributed to the stricter contraindication in treatment guidelines at the time, concerning the use of IFN-beta during pregnancy, and more conservative clinical practice (European Medicines Agency EMA, 2020b, European Medicines Agency EMA, 2020c). Since then and still during the study period (until 2014), more evidence has been published on the safety of IFN-beta use during pregnancy (Hellwig et al., 2012; Romero et al., 2015; Coyle et al., 2014; Sandberg-Wollheim et al., 2011; Amato et al., 2010; Weber--Schoendorfer and Schaefer, 2009; Patti et al., 2008), which has likely impacted clinicians' recommendations and maternal decision-making and led to a decreasing frequency of elective terminations over time. The high frequency of elective terminations for reasons other than foetal anomaly among the IFN-beta only exposed pregnancies also led to a high frequency of non-live births among the pregnancies exposed only to IFN-beta. The low number of stillbirths (also included in the definition of non-live births) hindered observing patterns in the prevalence of stillbirths.

These descriptive results indicate that none of the maternal characteristics had a statistically relevant impact as effect modifiers on the prevalence of adverse pregnancy outcomes among the pregnancies exposed only to IFN-beta. Thus, this study informs about the homogeneity and commonality of the effect that IFN-beta has when used during pregnancy regardless of the characteristics of the mother (Rothman



	Exposed		Unexposed	
	n/N	% CI (95%)	n/N	% CI (95%)
Country: Finland	1/295	0.3 (0.0 – 1.9)	4/474	0.8 (0.2 – 2.1)
Sweden	1/423	0.2 (0.0 – 1.3)	4/923	0.4 (0.1 – 1.1)
Year of pregnancy outcome: 1996–1999	0/1	0.0 (0.0 – 97.5)	0/44	0.0 (0.0 – 8.0)
2000–2004	0/26	0.0 (0.0 – 13.2)	0/32	0.0 (0.0 – 10.9)
2005–2009	0/207	0.0 (0.0 – 1.8)	2/468	0.4 (0.1 – 1.5)
>=2010	2/484	0.4 (0.1 – 1.5)	6/853	0.7 (0.3 – 1.5)
Maternal age at LMP (years): <=20	0/7	0.0 (0.0 – 41.0)	0/13	0.0 (0.0 – 24.7)
21–25	0/90	0.0 (0.0 – 4.0)	0/129	0.0 (0.0 – 2.8)
26–30	1/253	0.4 (0.0 – 2.2)	5/435	1.1 (0.4 – 2.7)
31–35	1/291	0.3 (0.0 – 1.9)	2/528	0.4 (0.0 – 1.4)
36–40	0/60	0.0 (0.0 – 6.0)	1/267	0.4 (0.0 – 2.1)
>40	0/17	0.0 (0.0 – 19.5)	0/25	0.0 (0.0 – 13.7)
Any chronic diseases: No	0/462	0.0 (0.0 – 0.8)	4/855	0.5 (0.1 – 1.2)
Yes	2/256	0.8 (0.1 – 2.8)	4/542	0.7 (0.2 – 1.9)
Exposure to group C teratogenic medications: No	0/249	0.0 (0.0 – 1.5)	3/664	0.5 (0.1 – 1.3)
Yes	2/469	0.4 (0.1 – 1.5)	5/733	0.7 (0.2 – 1.6)
Exposure to group D teratogenic medications: No	2/587	0.3 (0.0 – 1.2)	6/1226	0.5 (0.2 – 1.1)
Yes	0/131	0.0 (0.0 – 2.8)	2/171	1.2 (0.1 – 4.2)
Time since MS diagnosis at LMP (years): <=2	0/220	0.0 (0.0 – 1.7)	3/396	0.8 (0.2 – 2.2)
3–5	1/254	0.4 (0.0 – 2.2)	3/464	0.6 (0.1 – 1.9)
>5	1/244	0.4 (0.0 – 2.3)	2/537	0.4 (0.0 – 1.3)
Duration of MS treatment at LMP (years): <=2	0/302	0.0 (0.0 – 1.2)	4/475	0.8 (0.2 – 2.1)
3–5	1/229	0.4 (0.0 – 2.4)	0/349	0.0 (0.0 – 1.1)
>5	1/187	0.5 (0.0 – 2.9)	2/338	0.6 (0.1 – 2.1)
Never (no use)	0/0	NaN (NA – NA)	2/235	0.9 (0.1 – 3.0)
Total	2/718	0.3 (0.0 – 1.0)	8/1397	0.6 (0.2 – 1.1)

Fig. 2.4. Prevalence of *stillbirths* (IFN-beta only exposed N=718 pregnancies; unexposed N=1397 pregnancies) stratified by **maternal characteristics**, among pregnancies exposed only to IFN-beta 6 months or during pregnancy and among those unexposed to any MSDMDs.
CI, confidence interval; IFN-beta, interferon beta; LMP, last menstrual period; MS, multiple sclerosis; n, number of pregnancy outcome events.

et al., 2008).

Although we detected a numerically higher point prevalence of serious adverse pregnancy outcomes and MCAs among the IFN-beta exposed pregnancies of women treated for MS for >5 years before the pregnancy, compared to the pregnancies unexposed to any MSDMDs, the presence of effect modification by duration of MS treatment is unlikely. If the duration of MS treatment was an effect modifier, as defined by Rothman et al. (2008), the risk of serious adverse pregnancy outcomes and MCAs after IFN-beta exposure would vary across the strata by treatment duration. Our *post hoc* analyses with confounder adjustment did not support the presence of such effect modification, especially acknowledging probable residual confounding despite the confounder adjustment. Further, an increased risk of adverse outcomes in the pregnancies of women who were treated with IFN-beta during pregnancy and who had been for >5 years before pregnancy is unlikely based on medical plausibility, because these women are likely to have stable MS disease and be in good overall health.

4.2. Newborn characteristics

After stratification by newborn characteristics, our results were also consistent with the unstratified results in the same population (Hakkarainen et al., 2020), with no increased prevalence estimates among the exposed pregnancies. Although newborns born within 28-36 weeks of gestation had a numerically higher prevalence of MCAs and the composite serious adverse pregnancy outcomes in the IFN-beta exposed pregnancies, the result was based on few outcomes per stratum and the precision of the prevalence was low. Thus, it cannot be concluded that these outcomes would be more prevalent among the IFN-beta exposed pregnancies than the unexposed pregnancies when the child is born early. Irrespective of IFN-beta exposure, the study finding that the prevalence of MCA was higher in live births of earlier gestational age is biologically plausible and supported by literature (Honein et al., 2009).

4.3. Clinical significance

The stratified analysis results of this large cohort study mirror the unstratified findings in the same population (EPID Multiple Sclerosis Pregnancy study, 2020; Hakkarainen et al., 2020), that IFN-beta exposure before or during pregnancy does not appear to be harmful for the child. Thus, this study provides additional evidence on the safety of prescribing IFN-beta treatment for women with MS who are planning pregnancy, until the pregnancy is confirmed or even beyond, if the risk of relapse and disability accumulation during pregnancy needs to be reduced. The findings of this PASS cohort (EPID Multiple Sclerosis Pregnancy study, 2020, Hakkarainen et al., 2020) also led to a label change in the European Union, according to which IFN-beta products may now be considered during pregnancy, if clinically needed.

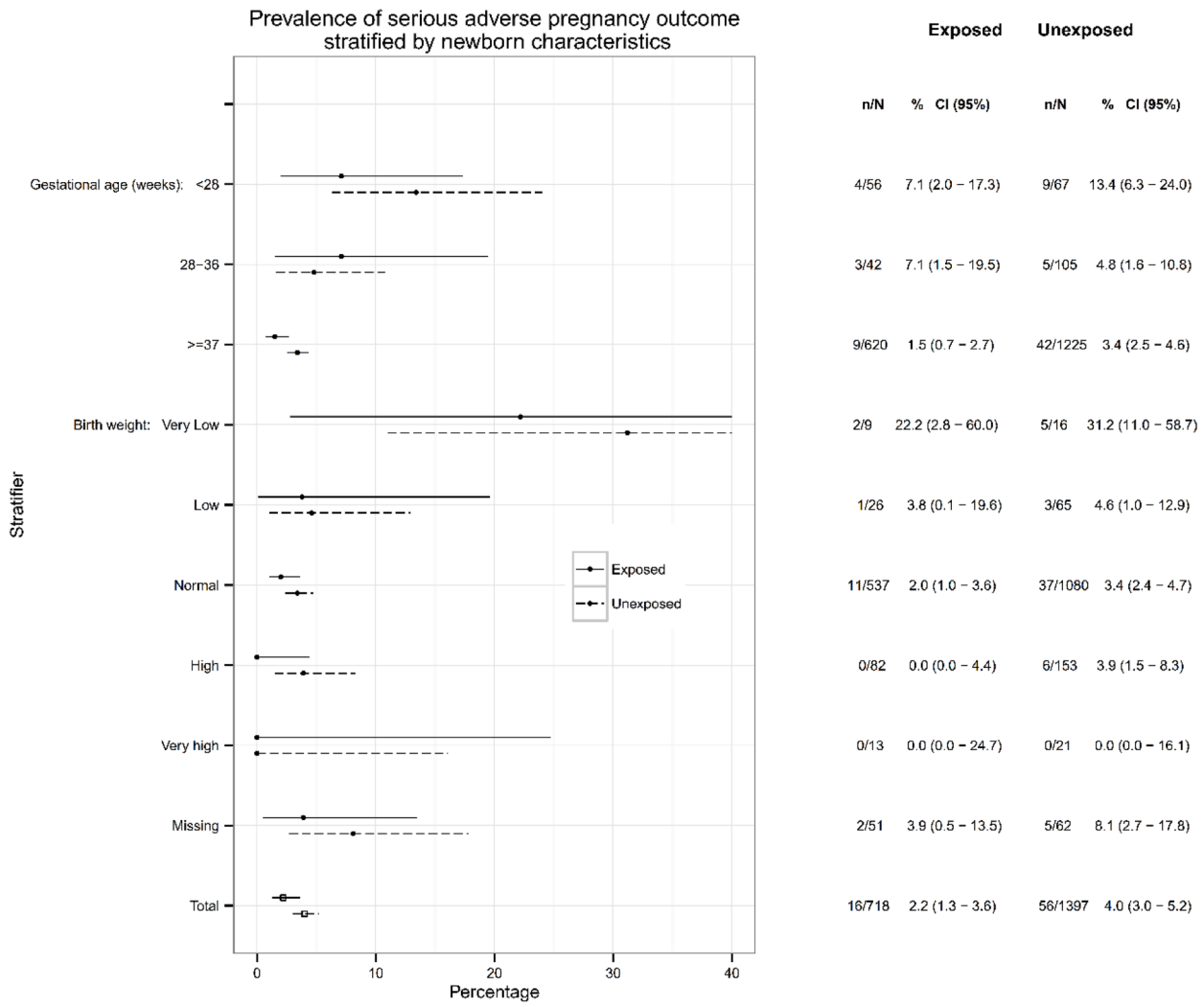


Fig. 3.1. Prevalence of *serious adverse pregnancy outcomes* (IFN-beta only exposed N=718 pregnancies; unexposed N=1397 pregnancies) stratified by **newborn characteristics**, among pregnancies exposed only to the IFN-beta 6 months before or during pregnancy and among those unexposed.
CI, confidence interval; IFN-beta, interferon beta; MS, multiple sclerosis; n, number of pregnancy outcome events.

The results obtained in this study can also be considered generalizable in the Nordic countries other than Finland and Sweden. This could be considered based on that maternal characteristics of pregnant women with MS are expected to be similar between the Nordic countries and that the Nordic countries have similar population structures, healthcare systems with universal healthcare (including free-of-charge maternal care), and are welfare societies with small socioeconomic differences. The results of the current study may not be fully generalizable to other countries and regions with differing maternal characteristics (e.g., a higher BMI, as found in the United Kingdom (Euro-Peristat Project, 2018)), population structures, healthcare systems, and societies consisting of people who share a different common culture. The results are likely more generalizable in countries similar to Finland and Sweden.

4.4. Methodological considerations

Our study is, the first in our knowledge to investigate the prevalence of adverse pregnancy outcomes among pregnant women with MS exposed and unexposed to IFN-beta, stratified by maternal and newborn characteristics. Our results are strengthened by the national coverage of the Finnish and Swedish registers, the inclusion of an exhaustive MS patient pool, high quality register data (Finnish Institute for Health and Welfare THL, 2020c), and the long study period that allowed inclusion of over 2,000 pregnancies. The stratified prevalences, however, should be interpreted with caution as the descriptive prevalences were not controlled for confounding in the main analyses, which should be considered as one of the study limitations. An additional limitation was the low number of pregnancies and outcomes in several strata, which limit us from drawing definite conclusions, especially for the least prevalent outcomes: elective TOPFA and stillbirths. More specifically, the absence of statistically significant findings was likely contributed by lack of statistical power. However, this study included the entire population of pregnancies matching our inclusion criteria, for both Finland and Sweden, reducing concerns relating to sample size, which in general applies to probability sampling rather than whole population studies. However, stratified analyses performed on larger populations could prove beneficial in order to confirm the findings of our study.

Our descriptive results are also strengthened by the *post-hoc* analyses with confounder adjustments, in which the only suspected effect modifier, 'duration of MS treatment', was not found to modify the risk of adverse pregnancy outcomes after IFN-beta exposure. Yet, the *post-hoc* analysis result should be interpreted with caution due to probable residual confounding despite adjusting for several important potential confounding factors, and due to the low number of pregnancies and outcomes.

An important limitation of this study is the exclusion of spontaneous

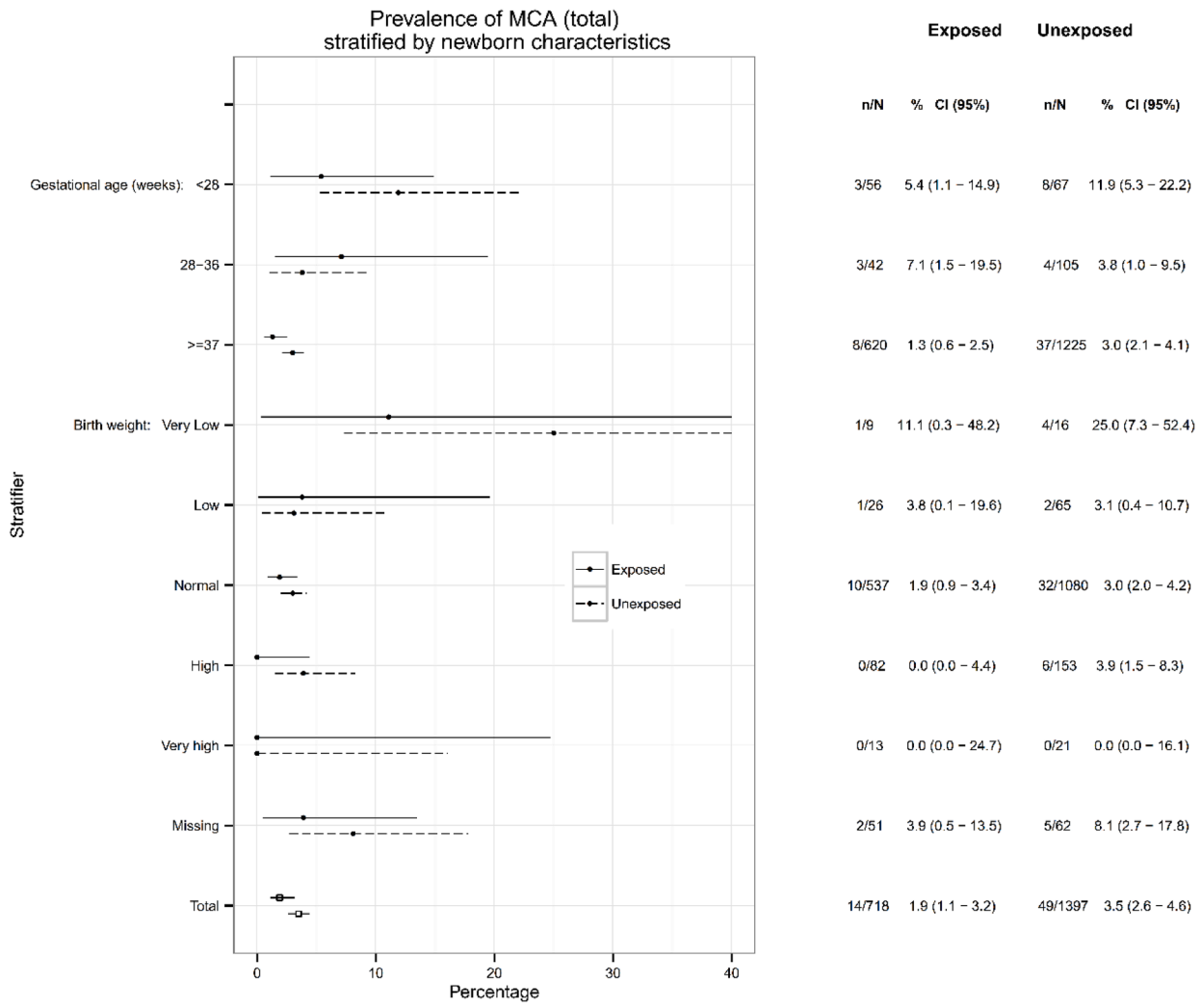


Fig. 3.2. Prevalence of *MCA total* (IFN-beta only exposed N=718 pregnancies; unexposed N=1397 pregnancies) stratified by **newborn characteristics**, among pregnancies exposed only to the IFN-beta 6 months before or during pregnancy and among those unexposed.
CI, confidence interval; IFN-beta, interferon beta; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy outcome events.

abortions from the stratification, as described under methods. However, the spontaneous abortions were analysed in the unstratified analysis and reported accordingly (EPID Multiple Sclerosis Pregnancy study, 2020; Hakkarainen et al., 2020). Our results were also limited by the unavailability of elective terminations in Sweden, as elective terminations were collected anonymously, without a possibility to link pregnancy outcomes to the exposure. Therefore, elective terminations were not available for analyses in any Swedish registers, which resulted in the descriptive prevalence generally appearing higher in Finland.

As described previously (Hakkarainen et al., 2020), the use of dispensing data hindered the ability to establish whether the dispensed drugs were used and to identify administered drugs in hospitals, including infusible therapies and study drugs such as mitoxantrone. The limitation was more pronounced in Finland, where exclusively dispensing data was used, while in Sweden administered drugs in hospitals could, to some extent, be detected from the MS Register. This limitation may have diluted possible differences in the outcome prevalence between the exposed and unexposed groups. However, a sensitivity analysis reported in the registered PASS (EPID Multiple Sclerosis Pregnancy study, 2020) revealed that the results of the unstratified analyses (Hakkarainen et al., 2020) remained consistent when all pregnancies with intravenous medical treatment administered in hospital were considered as exposed to other MSDMDs. Thus, this limitation did not hamper the conclusion of the PASS.

Additionally, the use of the register data hindered establishing whether the dispensed drugs were actually used and, as a consequence, also the exact length of exposure to IFN-beta that the women had during pregnancy. Additional *post-hoc* analyses (results not shown) revealed that in only 2-4% of the pregnancies, the women were dispensed IFN-beta during the second or third trimester. In the interpretation of this study, the results should primarily be interpreted to represent IFN-beta exposure before and in early pregnancy.

Further, the maternal characteristics in this study did not include variables on MS disease course and severity, such as Expanded Disability Status Scale (EDSS) score, because clinical variables on MS disease were available exclusively in Sweden (MS Register) at the time of designing the study, and these variables had also partial missingness. However, there is no rationale that differing MS disease course or EDSS alone would lead to adverse pregnancy outcomes (Thöne et al., 2017; Pozzilli et al., 2015), but might carry information on differing treatment approaches relevant for adverse pregnancy outcomes. Further information on the distribution of the included maternal characteristics in the unstratified population is available in the registered full study report (EPID Multiple Sclerosis Pregnancy study, 2020) and in the publication

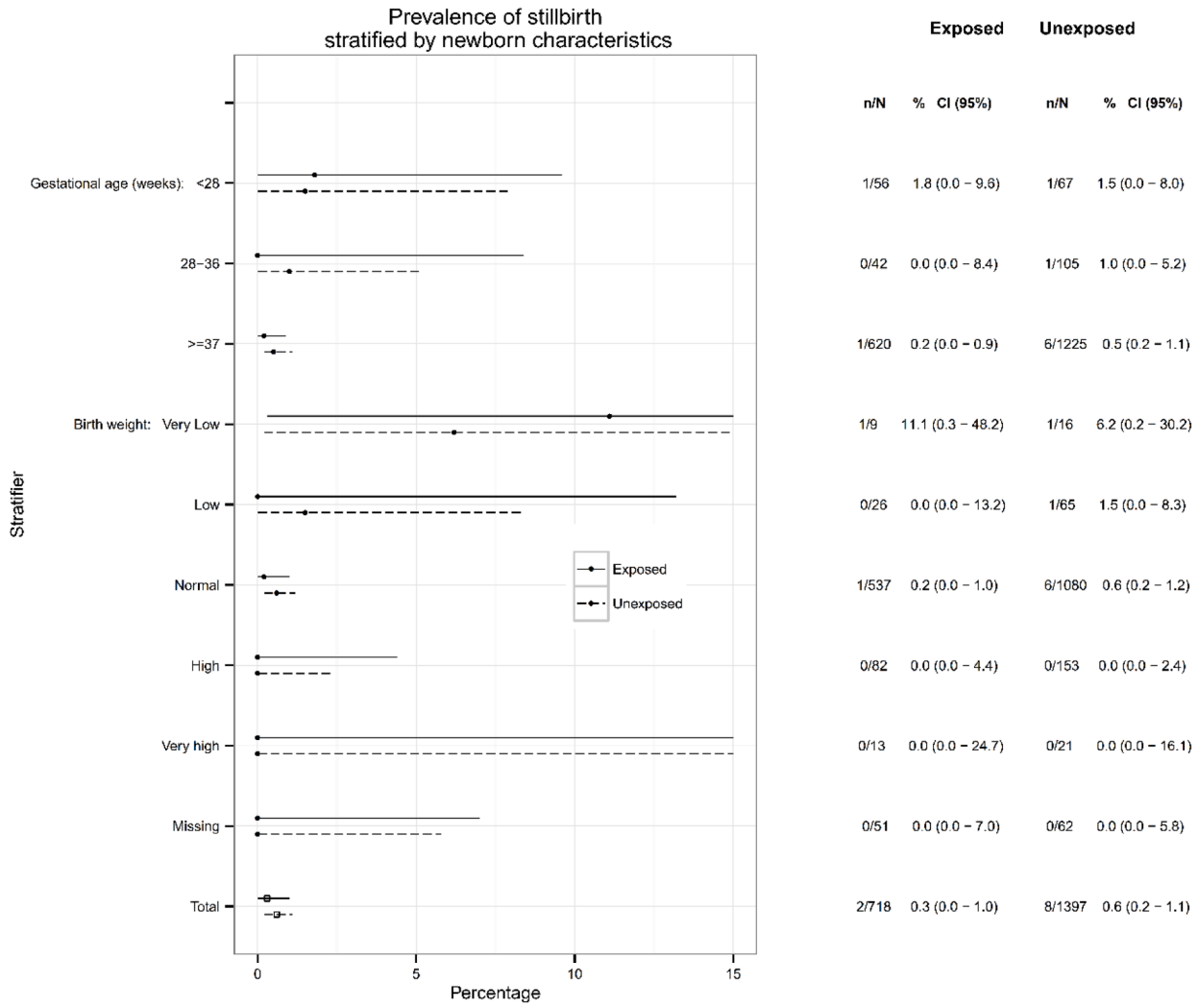


Fig. 3.3. Prevalence of *stillbirths* (IFN-beta only exposed N=718 pregnancies; unexposed N=1397 pregnancies) stratified by **newborn characteristics**, among pregnancies exposed only to the IFN-beta 6 months before or during pregnancy and among those unexposed.
CI, confidence interval; IFN-beta, interferon beta; MS, multiple sclerosis; n, number of pregnancy outcome events.

of unstratified analyses (Hakkarainen et al., 2020).

Finally, our study did not include the most recent years, due to the time required for accessing register data and conducting a large multi-country, multiple database study submitted to and reviewed by regulatory drug agencies.

5. Conclusion

The prevalence of adverse pregnancy outcomes was not increased after IFN-beta exposure before and during pregnancy, when pregnancies of women with MS were stratified by maternal and newborn characteristics. The stratified results were similar to the unstratified results in the same population.

Author statement

Marta Korjagina: Writing - Original Draft; Writing - Review & Editing, Visualisation; Project administration

Katja M Hakkarainen: Writing - Original Draft; Writing - Review & Editing; Methodology; Supervision,

Sarah Burkill: Formal analysis; Data Curation; Software; Writing - Review & Editing,

Yvonne Geissbühler: Conceptualisation; Methodology; Writing - Review & Editing,

Meritxell Sabidó: Conceptualisation; Methodology; Writing - Review & Editing,

Nicholas Everage: Conceptualisation; Methodology; Writing - Review & Editing,

Kiliana Suzart-Woischnik: Conceptualisation; Methodology; Writing - Review & Editing,

Riho Klement: Methodology; Formal analysis; Data Curation; Software; Writing - Review & Editing, Visualisation,

Jan Hillert: Writing - Review & Editing,

Auli Verkkoniemi-Ahola: Conceptualisation; Methodology; Writing - Review & Editing,

Shahram Bahmanyar: Conceptualisation; Methodology; Investigation; Writing - Review & Editing,

Scott Montgomery: Conceptualisation; Methodology; Writing - Review & Editing,

Pasi Korhonen: Conceptualisation; Methodology; Investigation; Writing - Review & Editing, Supervision

Disclosures

MK, KMH, RK are and **PK** was at the time of conducting the study employees of StatFinn and EPID Research which performs

commissioned pharmacoepidemiological studies for several pharmaceutical companies. **YG** is an employee of Novartis Pharma AG. **MS** is an employee of Merck KGaA, Darmstadt, Germany. **NE** is an employee and stockholder of Biogen. **KS-W** is an employee of Bayer AG. **JH** has received unrestricted grants, honoraria for serving on advisory boards and/or speaker honoraria from Biogen, Sanofi-Genzyme, Novartis, Merck-Serono, Bayer-Schering, Teva, and Biogen Idec. This MS research was funded by the Swedish Research Council and the Swedish Brain foundation. **AV-A** has received investigator fees (Sanofi) and congress fee covering or honoraria for lectures or advisory boards (Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, Grifols). **ShB** is and **SB** was at the time of conducting the study an employee at the Centre for Pharmacoepidemiology, which receive grants from several entities including pharmaceutical companies. **SM** has received funding for MS research in the last five years from Roche, Novartis, AstraZeneca; acted as study advisor for IQVIA; and speaker's honoraria, including from Teva.

Funding

This study was funded by Bayer AG, Biogen, Merck KGaA, and Novartis Europharm Limited.

Role of the funding source

The study sponsors could comment on the study design, the interpretation of data, and the writing of the manuscript. The study sponsors had no role in the data collection or analysis, or the decision to submit the paper for publication. The principal investigator PK confirms that he had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Acknowledgements

Non-author collaborators in the European Interferon Beta Pregnancy Study Group: Eva-Maria Wicklein (Bayer AG), Alessandra Adamo (Bayer AG), Metin Akbaba (Bayer AG), Gustavo Borghesi (Bayer AG), Evra Köfüncü (Bayer AG), Achint Kumar (Biogen), Catrinel Popescu (Biogen), Avni Pandhi (Biogen), Maria Naylor (Biogen), Anh Ly (EMD Serono Inc., a business of Merck KGaA, Darmstadt, Germany), Dominic Jack (Merck KGaA, Darmstadt, Germany), Milorad Todorovic (Merck KGaA, Darmstadt, Germany), Delphine Issard (Merck KGaA, Darmstadt, Germany), Alexandra Macklin (Novartis Pharma AG), Paola Primatesta (Novartis Pharma AG), Richard Weitzman (Novartis Pharma AG).

The Nordic MS Pregnancy & Interferon Beta study group: Rosa Juuti (StatFinn-EPID Research), Pia Vattulainen (StatFinn-EPID Research), Minna Vehkala (StatFinn-EPID Research), Juha Mehtälä (StatFinn-EPID Research), Hanna Gyllensten (StatFinn-EPID Research).

Credits: The representatives of the sponsors (Biogen, Bayer, Merck, Novartis) participated in revising the manuscript. We acknowledge Joosep Raudsik (StatFinn-EPID Research) as the project manager of this research project, and Paranjoy Saharia (IQVIA) for proof reading the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102694.

References

Amato, MP, Portaccio, E, Ghezzi, A, et al., 2010. Pregnancy and fetal outcomes after interferon-β exposure in multiple sclerosis. Neurology 75, 1794–1802. https://doi.org/10.1212/WNL.0b013e3181fd62bb.

Banwell, B, Ben-Zacharia, A, Bowen, J, et al., 2019. The use of disease-modifying therapies in Multiple Sclerosis. Principles and Current Evidence. A Consensus Paper by the Multiple Sclerosis Coalition.

Coyle, PK, Sinclair, SM, Scheuerle, AE, et al., 2014. Final results from the Betaseron (interferon β-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events. BMJ Open 4, e004536. https://doi.org/10.1136/bmjopen-2013-004536.

European Medicines Agency (EMA). Avonex - Summary of Product Characteristics [Internet], 2019a, https://www.ema.europa.eu/en/documents/product-information/avonex-epar-product-information_en.pdf (accessed 06 Nov 2020).

European Medicines Agency (EMA). Betaferon - Summary of Product Characteristics [Internet], 2019b, https://www.ema.europa.eu/en/documents/product-information/betaferon-epar-product-information_en.pdf (accessed 06 Nov 2020).

European Medicines Agency (EMA). Extavia- Summary of Product Characteristics [Internet], 2019c, https://www.ema.europa.eu/en/documents/product-information/extavia-epar-product-information_en.pdf (accessed 06 Nov 2020).

European Medicines Agency (EMA). Plegridy - Summary of Product Characteristics [Internet], 2019d, https://www.ema.europa.eu/en/documents/product-information/plegridy-epar-product-information_en.pdf (accessed 06 Nov 2020).

European Medicines Agency (EMA). Rebif - Summary of Product Characteristics [Internet], 2020a, https://www.ema.europa.eu/en/documents/product-information/rebif-epar-product-information_en.pdf (accessed 06 Nov 2020).

European Medicines Agency (EMA). Avonex - Procedural steps taken and scientific information after the authorisation [Internet], 2020b, https://www.ema.europa.eu/en/documents/procedural-steps-after/avonex-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf (accessed 19 Dec 2020).

European Medicines Agency (EMA). Betaferon - Procedural steps taken and scientific information after the authorisation [Internet], 2020c, https://www.ema.europa.eu/en/documents/procedural-steps-after/betaferon-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf (accessed 19 Dec 2020).

EPID Multiple Sclerosis Pregnancy study - Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon beta - a register-based study in the Nordic countries. http://www.encepp.eu/encepp/viewResource.htm?id=13055 (accessed 12 Jun 2020).

Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015 [Internet], 2018, https://www.europeristat.com/images/EPHR2015_Euro-Peristat.pdf (accessed 19 Dec 2020).

Finnish Institute for Health and Welfare (THL). Care Register for Health Care [Internet], 2016, http://thl.fi/fi/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care (accessed 19 Dec 2020).

Finnish Institute for Health and Welfare (THL). Medical Birth Register [Internet], 2019, http://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns (accessed 19 Dec 2020).

Finnish Institute for Health and Welfare (THL). Register of Induced Abortions [Internet], 2020a, https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/register-of-induced-abortions (accessed 19 Dec 2020).

Finnish Institute for Health and Welfare (THL). Register of Congenital malformations [Internet], 2020b, http://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/register-of-congenital-malformations (accessed 19 Dec 2020).

Finnish Institute for Health and Welfare (THL). Trends in access to specialised health care - Quality description [Internet], 2020c, http://thl.fi:8080/en/web/thlfi-en/statistics/information-on-statistics/quality-descriptions/trends-in-access-to-specialised-health-care (accessed 2 Jan 2020).

Hakkarainen, KM, Juuti, R, Burkill, S, et al., 2020. Pregnancy outcomes after exposure to interferon beta: a register-based cohort study among women with MS in Finland and Sweden. Ther. Adv. Neurol. Disord. 13, 1756286420951072 https://doi.org/10.1177/1756286420951072.

Hellwig, K, Duarte Caron, F, Wicklein, E-M, et al., 2020a. Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure. Ther. Adv. Neurol. Disord. 13. https://doi.org/10.1177/1756286420910310.

Hellwig, K, Geissbuehler, Y, Sabidó, M, et al., 2020b. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. J. Neurol. https://doi.org/10.1007/s00415-020-09762-y. Published Online First: 26 February.

Hellwig, K, Haghikia, A, Rockhoff, M, et al., 2012. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. Ther. Adv. Neurol. Disord. 5, 247–253. https://doi.org/10.1177/1756285612453192.

Hillert, J, Stawiarz, L., 2015. The Swedish MS registry – clinical support tool and scientific resource. Acta Neurol. Scand. 132, 11–19. https://doi.org/10.1111/ane.12425.

Honein, MA, Kirby, RS, Meyer, RE, et al., 2009. The association between major birth defects and preterm birth. Matern. Child Health J. 13, 164–175. https://doi.org/10.1007/s10995-008-0348-y.

Montalban, X, Gold, R, Thompson, AJ, et al., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur. J. Neurol. 25, 215–237. https://doi.org/10.1111/ene.13536.

National Board of Health and Welfare (Socialstyrelsen). The National Patient Register [Internet], 2019a, https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/ (accessed 06 Nov 2020).

National Board of Health and Welfare (Socialstyrelsen). The Swedish Medical Birth Register [Internet], 2019b, https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-medical-birth-register/ (accessed 06 Nov 2020).

Patti, F, Cavallaro, T, Lo Fermo, S, et al., 2008. Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? J. Neurol. 255, 1250–1253. https://doi.org/10.1007/s00415-008-0909-4.

Pozzilli, C, Pugliatti, M, Group, ParadigMS, 2015. An overview of pregnancy-related issues in patients with multiple sclerosis. Eur. J. Neurol. 22 (Suppl 2), 34–39. https://doi.org/10.1111/ene.12797.

Ransohoff, RM, Hafler, DA, Lucchinetti, CF., 2015. Multiple sclerosis-a quiet revolution. Nat. Rev. Neurol. 11, 134–142. https://doi.org/10.1038/nrneurol.2015.14.

Romero, RS, Lünzmann, C, Bugge, J-P., 2015. Pregnancy outcomes in patients exposed to interferon beta-1b. J. Neurol. Neurosurg. Psychiatry 86, 587–589. https://doi.org/10.1136/jnnp-2014-308113.

Rothman, Kenneth J., Greenland, Sander, Lash, Timothy L., 2008. Modern Epidemiology, 3rd ed. Lippincott Williams & Wilkins.

Sandberg-Wollheim, M, Alteri, E, Moraga, MS, et al., 2011. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. Mult. Scler. 17, 423–430. https://doi.org/10.1177/1352458510394610.

Social Insurance Institution (Kela). Statistics on reimbursement entitlements in respect of medicines [Internet], 2020a, https://www.kela.fi/en/web/en/statistics-by-topic/reimbursement-entitlements-in-respect-of-medicines (accessed 06 Nov 2020).

Social Insurance Institution (Kela). Statistics on reimbursements for prescription medicines [Internet], 2020b, https://www.kela.fi/web/en/statistics-by-topic/reimbursements-for-prescription-medicines (accessed 06 Nov 2020).

Thiel, S, Langer-Gould, A, Rockhoff, M, et al., 2016. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis-a prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. Mult. Scler. 22, 801–809. https://doi.org/10.1177/1352458516634872.

Thöne, J, Thiel, S, Gold, R, et al., 2017. Treatment of multiple sclerosis during pregnancy - safety considerations. Expert Opin. Drug Saf. 16, 523–534. https://doi.org/10.1080/14740338.2017.1311321.

Väisänen, H., 2015. The association between education and induced abortion for three cohorts of adults in Finland. Population Stud. 69, 373–388. https://doi.org/10.1080/00324728.2015.1083608.

Weber-Schoendorfer, C, Schaefer, C., 2009. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. Mult. Scler. 15, 1037–1042. https://doi.org/10.1177/1352458509106543.

Wettermark, B, Hammar, N, Fored, CM, et al., 2007. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol. Drug Saf. 16, 726–735. https://doi.org/10.1002/pds.1294.

World Health Organization, 2016. WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience. editor. World Health Organization, Geneva.